UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

21/JUL/2009

MEMORANDUM

Subject:	Name of Pesticide Product:	KIXOR® Herbicide Technical
	EPA File Symbol:	7969-ETL
	DP Barcode:	D349940
	Decision No.:	389161
	Action Code:	R010
	PC Code:	118203 BAS 800 H (Saflufenacil)

From: Rick J. Whiting, Biologist
Technical Review Branch (TRB)
Registration Division (7505P)

To: Kathryn Montague / Joanne Miller, RM Team 23
Herbicide Branch
Registration Division (7505P)

Applicant: BASF Corporation
Agricultural Products
P.O. Box 13528
Research Triangle Park, NC 27709-3528

FORMULATION FROM LABEL:

Active Ingredient(s):	% by wt
118203 BAS 800 H (Saflufenacil) [CAS No. 372137-35-4]	97.4
Inert Ingredient(s):	2.6
Total:	100.0%

ACTION REQUESTED: The Risk Manager requests: "This bean is for acute toxicology portion of the review of the new a.i. BAS 800-H (Saflufenacil). This is a joint review with Canada and Australia. Canada has lead on the acute toxicology, so EPA will be providing secondary review for this discipline."

BACKGROUND: BASF Corporation has submitted six acute toxicity studies, a Basic CSF dated December 19, 2007 and a proposed label to support the registration of KIXOR® Herbicide Technical (previously named BAS 800 H Herbicide Technical), EPA File Symbol 7969-ETL. The acute toxicity studies were conducted at Experimental Toxicology and Ecology and assigned MRID numbers 471281-01 thru -07. The Pest Management Regulatory Agency –Health Canada (PMRA) conducted the primary review of the studies. TRB performed the secondary review and made changes as necessary.

COMMENTS AND RECOMMENDATIONS:

1. The six studies have been reviewed and are classified as acceptable.

2. The acute toxicity profile for KIXOR® Herbicide Technical, EPA File Symbol 7969-ETL, is as follows:

Acute oral toxicity	III	Acceptable	MRID 47128101
Acute dermal toxicity	III	Acceptable	MRID 47128102
Acute inhalation toxicity	IV	Acceptable	MRID 47128103
Primary eye irritation	IV	Acceptable	MRID 47128104
Primary eye irritation	IV	Acceptable	MRID 47128105
Primary skin irritation	IV	Acceptable	MRID 47128106
Dermal sensitization	Negative	Acceptable	MRID 47128107

3. Based on the toxicity profile above, the following are the precautionary and first aid statements for this product as obtained from the Label Review System:

PRODUCT ID #: 007969-00275

PRODUCT NAME: KIXOR® Herbicide Technical

PRECAUTIONARY STATEMENTS

SIGNAL WORD: CAUTION

Hazards to Humans and Domestic Animals:

Harmful if absorbed through skin. Harmful if swallowed. Avoid contact with skin, eyes or clothing. Wash thoroughly with soap and water after handling and before eating, drinking, chewing gum, or using tobacco. Wear long-sleeved shirt and long pants, socks, shoes, and gloves. Remove and wash contaminated clothing before reuse.

First Aid:

If on skin: Take off contaminated clothing. Rinse skin immediately with plenty of water for 15-20 minutes. Call a poison control center or doctor for treatment advice.

If swallowed: Call a poison control center or doctor immediately for treatment advice. Have person sip a glass of water if able to swallow. Do not induce vomiting unless told to by a poison control center or doctor. Do not give anything to an unconscious person.

Have the product container or label with you when calling a poison control center or doctor or going for treatment. You may also contact 1-800-xxx-xxxx for emergency medical treatment information.

4. In addition, TRB noted that the registrant has included additional First Aid statements. TRB finds this additional labelling information acceptable.

5. The Basic Formulation CSF (dated December 19, 2007) for the proposed product should also be reviewed and accepted by the TRB Chemistry Team.

Primary Reviewer: Steve Wong, Ph.D., PMRA **Date: March 6, 2008**
Secondary Reviewer: Rick Whiting, EPA
Risk Manager (EPA): 23

STUDY TYPE: Acute Oral Toxicity – Rat; OPPTS 870.1100; OECD 423

TEST MATERIAL: BAS 800 H; 93.8% a.i.; Batch No. COD-000515; light beige solid

CITATION: Gamer, A.O., Leibold, E. (2005) BAS 800 H: Acute oral toxicity study in rats. Study No. 10A0414/011124. Unpublished study by Experimental Toxicology and Ecology, BASF Aktiengesellschaft, Germany. August 8, 2005. MRID 47128101.

SPONSOR: BASF Corporation, Agricultural Products Division, RTP, NC 27709

EXECUTIVE SUMMARY: In an acute oral toxicity study (MRID 47128101), six fasted adult female Wistar / HanRcc:WIST(SPF) rats were given a single oral gavage dose of 2000 mg/kg/bw BAS 800 H (93.8% a.i.; Batch No. COD-0005151) prepared in 0.5% CMC-solution in doubly distilled water and observed for 14 days. The animals were approximately 8-12 weeks old (166-192 g) and supplied by RCC Ltd Laboratory Animal Services, Switzerland.

No mortality occurred in the study and no clinical signs were observed. Body weight increased throughout the study. No gross abnormalities were observed in the animals.

LD_{50} Females > 2000 mg/kg bw

Based on the acute oral LD_{50}, BAS 800 H was classified as EPA Toxicity Category III.

This study is classified as acceptable. It does satisfy the guideline requirements for an acute oral study (OPPTS 870.1100; OECD 423) in the rat.

COMPLIANCE: Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. **Test Material:** BAS 800 H (N'-[2-chloro-4-fluoro-5-(3-methyl-2,6-dioxo-4-(trifluoromethyl) -3,6-dihydro-1(2H)-pyrimidinyl)benzoyl]-N-isopropyl-N-methylsulfamide)

Description:	Solid, light beige
Lot/Batch #:	COD-000515
Purity:	93.8% a.i.
CAS # TGAI:	372137-35-4

The stability of the test substance in the vehicle for the maximum application period was confirmed by analytical verification of the dosing solution concentration. The homogeneity of the test substance preparation in the vehicle used for the first administration was confirmed indirectly by the concentration control analysis. The concentration of the test substance preparation in the vehicle for the first administration was confirmed by analysis. (Details are available in the raw data.)

2. Vehicle and/or positive control: The test substance preparation (test substance in 0.5% CMC solution in doubly distilled water) was produced for each administration group shortly before administration by stirring with a high speed homogenizer (Ultra-Turrax) and a magnetic stirrer.

3. **Test animals:**

Species:	Rat, ♀	
Strain:	Wistar/HansRcc:WIST(SPF)	
Age/weight at dosing:	Age: 8 – 12 weeks; nulliparous and non-pregnant Mean body weight: 189 and 171 g for administration 1 and 2 respectively	
Source:	RCC Ltd Laboratory Animal Services, Wölferstrasse 4, CH-4414 Füllinsdorf, Switzerland	
Housing:	Singly in stainless steel wire mesh cages, type DK-III (Becker & Co., Castrop-Rauxel, FRG)	
Diet:	Kliba-Labordiat (Maus/Ratte Haltung "GLP"), Provimi Kliba SA, Kaiseraugst, Basel Switzerland, *ad libitum*	
Water:	Tap water *ad libitum*	
Environmental conditions:	**Temperature:**	20 -24°C
	Humidity:	30 - 70%
	Air changes:	10 air changes/h
	Photoperiod:	12 h dark/ 12 h light
Acclimation period:	At least 5 days before application	

B. STUDY DESIGN and METHODS:

1. In life dates - Start: March 15, 2005 End: May 10, 2005

2. Animal assignment and treatment – Animals were assigned to the test groups noted in Table 1. Following an overnight fast (≥16 hours), rats were given a single dose of BAS 800 H by gavage, then observed daily and weighed shortly before administration, weekly thereafter and at the end of the study (14 days). Survivors were sacrificed and a gross necropsy was performed.

Table 1. Doses, mortality/animals treated

Dose, mg/kg bw	♀ (test 1)	♀ (test 2)	♀ (combined test 1 & 2)
2000	0/3	0/3	0/6

3. Statistics - The oral LD_{50} was not statistically calculated, since this was a limit test.

II. RESULTS AND DISCUSSION:

A. Mortality – There were no deaths. The oral LD_{50} for females was >2000 mg/kg bw.

B. Clinical observations - There were no deaths or clinical signs observed on the study.

C. Body weight - All animals gained weight during the study.

D. Necropsy - No macroscopic pathologic abnormalities were noted at the end of the study.

E. Authors' conclusions: *"Under the conditions of this study, the median lethal dose of BAS 800 H after oral administration was found to be greater than 2,000 mg/kg body weight in female rats."*

F. Deficiencies: None.

Primary Reviewer: Steve Wong, Ph.D., PMRA **Date: March 6, 2008**
Secondary Reviewer: Rick Whiting, EPA
Risk Manager (EPA): 23

STUDY TYPE: Acute Dermal Toxicity – Rat; OPPTS 870.1200; OECD 402

TEST MATERIAL: BAS 800 H; 93.8% a.i.; Batch No. COD-000515; light beige solid

CITATION: Gamer, A.O., Leibold, E. (2005) BAS 800 H: Acute dermal toxicity study in rats. Study No. 11A0414/011125. Unpublished study by Experimental Toxicology and Ecology, BASF Aktiengesellschaft, Germany. August 8, 2005. MRID 47128102.

SPONSOR: BASF Corporation, Agricultural Products Division, RTP, NC 27709

EXECUTIVE SUMMARY: In an acute dermal toxicity study (MRID 47128102), a group of five male and five female Wistar / HanRcc:WIST(SPF) rats was dermally exposed to BAS 800 (93.8% a.i.; Batch No. COD-0005151) applied at a dose of 2000 mg/kg bw for 24 hours. The test material was prepared in 0.5% CMC-solution in doubly distilled water. The dose (dry paste) was applied to the clipped skin (approximately 40 cm^2, at least 10% of body surface) on the dorsal and dorsolateral parts of the trunk and covered by a semi-occlusive dressing for 24 hours. The dressing consisted of four layers of absorbent gauze and Fixomull stretch adhesive fleece. After 24 hours, the dressings were removed and the site gently cleansed of any remaining test material with warm water. The animals were then observed for 14 days. The animals were approximately 8-14 weeks old (males: 8-10 weeks, 266-279 g; females: 12-14 weeks, 209-226 g) and supplied by RCC Ltd Laboratory Animal Services, Switzerland.

No mortality occurred and no systemic clinical observations or skin effects were noted in the animals. Body weight increased throughout the study. No gross abnormalities were found in the animals.

LD_{50} Males > 2000 mg/kg bw
LD_{50} Females > 2000 mg/kg bw
LD_{50} Combined > 2000 mg/kg bw

Based on the acute dermal LD_{50}, BAS 800 H was classified as EPA Toxicity Category III.

This study is classified as acceptable. It does satisfy the guideline requirements for an acute dermal study (OPPTS 870.1200; OECD 402) in the rat.

COMPLIANCE: Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. **Test material:** BAS 800 H (N'-[2-chloro-4-fluoro-5-(3-methyl-2,6-dioxo-4-(trifluoromethyl)-3,6-dihydro-1(2H)-pyrimidinyl)benzoyl]-N-isopropyl-N-methylsulfamide)
   Description: Solid, light beige
   Lot/Batch #: COD-000515
   Purity: 93.8% a.i.
   CAS # TGAI: 372137-35-4
   The homogeneity of the test material was confirmed by analysis. The stability under the storage conditions over the study period was guaranteed by the Certificate of Analysis.

2. **Vehicle and/or positive control:** The test substance preparation (test substance in 0.5% CMC solution in doubly distilled water) was produced shortly before administration by stirring with pestle and mortar.

3. **Test animals:**

Species:	Rat	
Strain:	Wistar (HansRcc:WIST(SPF)	
Age/weight at dosing:	Age: ♂ = 8 - 10 weeks; ♀ = 12 -14 weeks; female animals were nulliparous and non-pregnant Mean weight: ♂ = 273 g; ♀ = 216 g	
Source:	RCC Ltd Laboratory Animal Services, Wölferstrasse 4, CH-4414 Füllinsdorf, Switzerland	
Housing:	Singly in stainless steel wire mesh cages, type DK-III (Becker & Co., Castrop-Rauxel, FRG)	
Diet:	Kliba-Labordiat (Maus/Ratte Haltung "GLP"), Provimi Kliba SA, Kaiseraugst, Basel Switzerland, *ad libitum*	
Water:	Tap water *ad libitum*	
Environmental conditions:	**Temperature:**	20 - 24°C
	Humidity:	30 – 70%
	Air changes:	10 air changes/h
	Photoperiod:	12 h dark/12 h light
Acclimation period:	At least 5 days	

B. STUDY DESIGN and METHODS:

1. **In life dates** - Start: March 15, 2005 End: March 30, 2005

2. Animal assignment and treatment – Animals were assigned to the test groups noted in Table 1. Animals were given a single dose of BAS 800 H dermally to the clipped skin (dorsal and dorsolateral parts of the trunk). The application site (about 40 cm^2, corresponding to at least 10% of the body surface) was covered with a semi-occlusive dressing (four layers absorbent gauze and adhesive fleece) for 24 hours. After the removal of the dressing, the application site was rinsed with warm water. The rats were observed daily and weighed shortly before dosing, weekly thereafter and at the end of the study. Survivors were sacrificed and a necropsy was performed.

Table 1. Doses, mortality/animals treated

Dose (mg/kg bw)	♂	♀	♂♀
2000	0/5	0/5	0/10

3. Statistics - Statistics were not run in this study, since there was no mortality at the limit dose.

II. RESULTS AND DISCUSSION:

A. Mortality – There were no deaths. The dermal LD_{50} for males, females, and combined is >2000 mg/kg bw.

B. Clinical observations - There were no deaths or clinical signs observed on the study.

C. Body weight - All animals gained weight during the study.

D. Necropsy – No macroscopic pathologic abnormalities were noted at the end of the study.

E. Authors' conclusions: *"Under the conditions of this study, the median lethal dose of BAS 800 H after dermal application was found to be greater than 2000 mg/kg body weight in male and female rats."*

F. Deficiencies: None.

Primary Reviewer: Steve Wong, Ph.D., PMRA **Date: March 6, 2008**
Secondary Reviewer: Rick Whiting, EPA
Risk Manager (EPA): 23

STUDY TYPE: Acute Inhalation Toxicity – Rat; OPPTS 870.1300; OECD 403

TEST MATERIAL: BAS 800 H; 93.8% a.i.; Batch No. COD-000515; light beige solid; expiry date: February 1, 2006

CITATION: Ma-Hock, L., Leibold, E. (2005) BAS 800 H: Acute inhalation toxicity study in Wistar rats. Study No. 13I0414/017021. Unpublished study by Experimental Toxicology and Ecology, BASF Aktiengesellschaft, Germany. August 30, 2005. MRID 47128103.

SPONSOR: BASF Corporation, Agricultural Products Division, RTP, NC 27709

EXECUTIVE SUMMARY: In an acute inhalation toxicity study (MRID 47128103), a group of five male and five female Wistar / HanRcc:WIST(SPF) rats (5/sex/group) was exposed by nose-only inhalation for 4 hours to 5.3 mg/L to BAS 800 H (93.8% a.i.; Batch No. COD-000515), as a dust aerosol. The mean gravimetric concentration for the test group was 5.3 mg/L, and the mass median aerodynamic diameters (MMAD) were 2.3 and 3.2 μm, and the gravimetric standard deviations (GSD) were 2.5 and 3.7 for two samples measured. The animals were observed for 14 days. The animals were 7-9 weeks old (males: 7 weeks, 201.8-228.7 g; females: 9 weeks, 187.3-193.5 g) and supplied by RCC Ltd Laboratory Animal Services, Switzerland.

No mortality occurred at 5.3 mg/L. Clinical signs of toxicity consisted of visually increased respiration, squatting posture, smeared and contaminated fur on all animals, and piloerection. Findings were observed from hour 0 of exposure through day 3. All animals gained weight throughout the study. No gross abnormalities were observed during necropsy.

LC_{50} Males > 5.3 mg/L
LC_{50} Females > 5.3 mg/L
LC_{50} Combined > 5.3 mg/L

Based on the 4-hour inhalation exposure LC_{50}, BAS 800 H was classified as EPA Toxicity Category IV.

This study is classified as acceptable. It does satisfy the guideline requirements for an acute inhalation study (OPPTS 870.1300; OECD 403) in the rat.

COMPLIANCE: Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. **Test material:** BAS 800 H (N'-[2-chloro-4-fluoro-5-(3-methyl-2,6-dioxo-4-(trifluoromethyl)-3,6-dihydro-1(2H)-pyrimidinyl)benzoyl]-N-isopropyl-N-methylsulfamide)

   Description: Solid, light beige; stored at room temperature

   Lot/Batch #: COD-000515

   Purity: 93.8% a.i.

   CAS #: 372137-35-4

   The homogeneity of BAS 800 H was confirmed by analysis. The stability under the storage conditions over the study period was guaranteed by the Certificate of Analysis.

2. **Vehicle and/or positive control:** The test substance was stirred in its container before a sample for dust generation was taken. The test substance was deagglomerated in a mixer under addition of 1% (w/w) of Aerosil 200 before introduction into the dust generator (dosing-wheel dust generator, Gericke/BASF), in order to improve dust aerosol formation.

3. **Test animals:**

Species:	Rat	
Strain:	Wistar (HansRcc:WIST(SPF)	
Age/weight at dosing:	Age: ♂ ~7 weeks; ♀ ~9 weeks; females were nulliparous and non-pregnant Weight: ♂ = 201.8 – 228.7 g; ♀ = 187.3 – 193.5 g	
Source:	RCC Ltd Laboratory Animal Services, Wölferstrasse 4, CH-4414 Füllinsdorf, Switzerland	
Housing:	Single housing; cages type DK III without bedding	
Diet:	KLIBA mouse / rat laboratory diet 10 mm pellets "GLP", Provimi Kliba SA, Kaiseraugst, Basel Switzerland *ad libitum*	
Water:	Tap water *ad libitum*	
Environmental conditions:	**Temperature:**	20- 24°C
	Humidity:	30 - 70%
	Air changes:	10 air changes/h
	Photoperiod:	12 h dark/12 h light
Acclimation period:	At least one week before the beginning of the study.	

B. STUDY DESIGN and METHODS:

1. **In life dates** - Start: June 14, 2005 End: June 28, 2005

2. Exposure conditions - The following mean values for exposure parameters were obtained.

Supply air, m^3/h	Exhaust air, m^3/h	Air flow, g/h*	Temperature, °C	Relative Humidity (%)
1.5	1.35	60.0	22.2 ± 0.3	47.6 ± 2.6

*Not corrected for 1% (w/w) Aerosil 200.

3. Animal assignment and treatment – Five male and five female rats were assigned to the test groups noted in Table 1. Rats were exposed to BAS 800 H by nose only for 4 hours. The rats were weighed just before exposure, weekly thereafter and at the end of the observation period. They were checked for overt clinical signs of toxicity or mortality twice a day on workdays and once daily on weekends and on holidays. Survivors at study termination were sacrificed and a necropsy was performed.

Table 1. Concentrations, exposure conditions, mortality/animals treated

Concentration, mg/L		MMAD, µm	GSD	Mortality/ # dead/# tested		
Nominal	Cctual			♂	♀	♂♀
40.0	5.3±0.14	2.3 & 3.2	2.5 -3.7	0/5	0/5	0/10

4. Generation of the test atmosphere / chamber description: A head-nose inhalation system INA 20 (glass-steel construction, BASF AG, volume ≈ 55 L) was used. The rats were restrained in glass tubes and their snouts projected into the inhalation chamber. The test substance dust was produced inside the inhalation system with the dust generator and compressed air.

The exposure system was located inside an exhaust cabin in an air-conditioned laboratory. A supply air flow (compressed air) of 1.5 m^3/h was used. The exhaust airflow was set to 1.35 m^3/h. An air change of about 27 times per hour can be calculated by dividing the supply air flow by the volume of the inhalation system. The lower amount of exhaust air, which was adjusted by means of a separate exhaust air system, achieved a positive pressure inside the exposure system. This ensured that the mixture of test substance and air was not diluted with laboratory air in the breathing zones of the animals.

The rats were exposed to the inhalation atmosphere for 4 hours plus equilibration time of the inhalation systems (t_{99} about 10 min.)

Nominal concentration: The nominal concentration was calculated from the amount of substance dosed and the supply air flow.

Gravimetric determination: Pre-weighed filters were placed into the filtration equipment. By means of the vacuum pump metered volumes of the dust were drawn through the filter. For each sample the dust aerosol concentration in mg/L was calculated from the difference between the preweight of the filter and the weight of the filter after sampling, with reference to the sample volume of the inhalation atmospheres. Mean and standard deviation were calculated for the concentration from the results of the individual measurements. The mean concentration was corrected for the amount of additive used.

Particle size analysis: Before sampling, the impactor was assembled with pre-weighed glass-fiber collecting discs, and a backup particle filter. The impactor was connected to the vacuum pump and two samples were taken from the breathing zone of the animals starting not earlier than 30 minutes after the beginning of the exposure. The sample volume was 6 L. After sampling the impactor was taken apart. The collecting discs and the backup particle filter were re-weighed. The amounts of material adsorbed to the walls of the impactor and in the sampling probe (wall losses) were also determined quantitatively. The results from the particle size analysis were not corrected for the additive.

5. Statistics - The LC_{50} was calculated using the binomial test.

II. RESULTS AND DISCUSSION:

A. Mortality and LC_{50} determination - No mortality occurred at the tested concentration. The LC_{50} for males, females and combined was >5.3 mg/L.

B. Clinical observations – Clinical signs of toxicity comprised squatting posture, piloerection, visually accelerated respiration and smeared and contaminated fur in all animals. Findings were observed from hour 0 of exposure until including study day 3.

C. Body weight - The mean body weights of the male and female animals increased throughout the post exposure observation period.

D. Necropsy - No gross pathological abnormalities were noted at study termination.

E. Authors' conclusions: *"Under the conditions of this study, the LC_{50} for male and female rats after dust inhalation was estimated to be > 5.3 mg/L."*

F. Deficiencies: None.

Primary Reviewer: Steve Wong, Ph.D., PMRA **Date: March 10, 2008**
Secondary Reviewer: Rick Whiting, EPA
Risk Manager (EPA): 23

STUDY TYPE: Primary Eye Irritation – Rabbit; OPPTS 870.2400; OECD 405

TEST MATERIAL: BAS 800 H; 93.9% a.i.; Batch No. COD-000298; light beige solid; stored at room temperature

CITATION: Remmele, M., Leibold, E. (2005) BAS 800 H: Acute eye irritation in rabbits. Study No. 11H0414/102297. Unpublished study by Experimental Toxicology and Ecology, BASF Aktiengesellschaft, Germany. May 9, 2005. MRID 47128104.

SPONSOR: BASF Corporation, Agricultural Products Division, RTP, NC 27709

EXECUTIVE SUMMARY: In a primary eye irritation study (MRID 47128104), 0.1 mL bulk volume of BAS 800 H (93.9% a.i.; Batch No. COD-000298), powdered solid, was instilled into the conjunctival sac of the right eye of two male and one female New Zealand White rabbits, and the upper and lower lids were held shut for approximately one second. The eyes were rinsed with warm tap water 1 hour after application using a syringe with a blunt probe. Eyes were scored for ocular irritation 1, 24, 48, and 72 hours after instillation. The untreated left eye of each animal served as a control. The animals were 5-6 months old (3.21 -3.47 kg), and supplied by Centre Lago S.A., France.

Slight or moderate conjunctival redness (grade 1 or 2) was observed in all treated eyes up to 24 hours after application. Slight conjunctival chemosis (grade 1) was noted in one animal and slight discharge (grade 1) was seen in all animals 1 hour after application. In addition, injected scleral vessels in a circumscribed area were observed in almost all animals up to 24 hours. The ocular reactions were reversible in all animals within 48 hours after application. Mean scores calculated for each animal over 24, 48, and 72 hours were 0.0 for corneal opacity, for iris lesions, and for chemosis, and 0.3 for redness of the conjunctiva, respectively.

Using the individual scores presented in the Report, the mean irritation scores (MIS) and the maximum average score (MAS, mean of 24, 48, and 72 h scores) are as follows: MIS (maximum = 110) at 1, 24, 48, and 72 h were 6, 3, 0, and 0, respectively; MAS (maximum = 110) was 1.

In this study, the formulation was practically non-irritating. BAS 800 H is classified as EPA Toxicity Category IV for primary eye irritation.

This study is classified as acceptable. It does satisfy the guideline requirements for a primary eye irritation study (OPPTS 870.2400; OECD 405) in the rabbit.

COMPLIANCE: Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. **Test material:** BAS 800 H (N'-[2-chloro-4-fluoro-5-(3-methyl-2,6-dioxo-4-(trifluoromethyl)-3,6-dihydro-1(2H)-pyrimidinyl)benzoyl]-N-isopropyl-N-methylsulfamide)

Description:	Solid, crystalline/light beige; stored at room temperature; pH (10% aqueous preparation) ≈ 4
Lot/Batch #:	COD-000298
Purity:	93.9 % a.i.
CAS #:	372137-35-4
	The homogeneity of BAS 800 H was confirmed by analysis. The stability under the storage conditions over the study period was guaranteed by the Certificate of Analysis.

2. Vehicle and/or positive control: No vehicle or positive control was used. The test substance was pulverized.

3. Test animals:

Species:	Rabbit (two males and one female)	
Strain:	New Zealand white A 1077 INRA (SPF)	
Age/weight at dosing:	Age: 5 - 6 months; Weight: ♂ = 3.21, 3.43 kg; ♀ = 3.47 kg	
Source:	Centre Lago S.A., 01540 Vonnas, France	
Housing:	Singly in stainless steel wire mesh cages with grating, floor area: 3000 cm^2	
Diet:	Kliba-Labordiat (Kaninchen & Meerschweinchenhaitung "GLP"), Provimi Kliba SA, Kaiseraugst, Basel Switzerland (about 130 g/animal per day)	
Water:	Tap water *ad libitum*	
Environmental conditions:	**Temperature:**	20 – 24°C
	Humidity:	30 - 70%
	Air changes:	10 air changes/h
	Photoperiod:	12 h dark/12 h light
Acclimation period:	At least 5 days before the beginning of the study.	

B. STUDY DESIGN and METHODS:

1. In life dates - Start: November 9, 2004 End: November 18, 2004

2. Animal assignment and treatment – Before the beginning of application both eyes were examined for signs of pre-existing irritation. Only rabbits with intact cornea and conjunctiva were used. At dosing, an amount of 0.1 mL (~32 mg) of BAS 800 H was instilled into the conjunctival sac of the right eye of three White New Zealand rabbits (stepwise procedure starting with one animal and supplementing two additional animals). About one hour after application, the eye was rinsed with tap water. Ocular reactions were assessed at approximately 1, 24, 48, and 72 hours after application.

II. RESULTS AND DISCUSSION:

A. Irritation findings: Slight or moderate conjunctival redness (grade 1 or 2) was observed in all treated eyes up to 24 hours after application. Slight conjunctival chemosis (grade 1) was noted in one animal and slight discharge (grade 1) was seen in all animals 1 hour after application. In addition, injected scleral vessels in a circumscribed area were observed in almost all animals up to 24 hours. The ocular reactions were reversible in all animals within 48 hours after application. Mean scores calculated for each animal over 24, 48, and 72 hours were 0.0 for corneal opacity, for iris lesions, and for chemosis, and 0.3 for redness of the conjunctiva, respectively.

	Number "positive"/number tested			
	Hours			
Observations	**1**	**24**	**48**	**72**
Corneal Opacity	0/3	0/3	0/3	0/3
Iritis	0/3	0/3	0/3	0/3
Conjunctivae:				
Redness*	2/3	0/3	0/3	0/3
Chemosis*	0/3	0/3	0/3	0/3
Discharge*	3/3	0/3	0/3	0/3

*Score of 2 or more required to be considered "positive."

B. Authors' conclusions: *"Considering the described ocular reactions as well as the average score for irritation, BAS 800 H does not show an eye irritation potential under the test conditions chosen."*

C. Reviewer's comments: Using the individual scores presented in the Report, the mean irritation scores (MIS) and the maximum average score (MAS, mean of 24, 48, and 72 h scores) are as follows: MIS (maximum = 110) at 1, 24, 48, and 72 h were 6, 3, 0, and 0, respectively; MAS (maximum = 110) was 1.

D. Deficiencies: None.

Primary Reviewer: Steve Wong, Ph.D., PMRA **Date: March 10, 2008**
Secondary Reviewer: Rick Whiting, EPA
Risk Manager (EPA): 23

STUDY TYPE: Primary Eye Irritation – Rabbit; OPPTS 870.2400; OECD 405

TEST MATERIAL: BAS 800 H; 93.8% a.i.; Batch No. COD-000515; light beige solid; stored at room temperature

CITATION: Remmele, M., Landsiedel, R. (2007) BAS 800 H: Acute eye irritation in rabbits. Study No. 11H0414/012309. Unpublished study by Experimental Toxicology and Ecology, BASF Aktiengesellschaft, Germany. May 3, 2007. MRID 47128105.

SPONSOR: BASF Corporation, Agricultural Products Division, RTP, NC 27709

EXECUTIVE SUMMARY: In a primary eye irritation study (MRID 47128105), 0.1 mL bulk volume of BAS 800 H (93.8% a.i.; Batch No. COD-000515), powdered solid, was instilled into the conjunctival sac of the right eye of two male and one female New Zealand White rabbits, and the upper and lower lids were held shut for approximately one second. The eyes were rinsed with warm tap water 24 hour after application using a syringe with a blunt probe. Eyes were scored for ocular irritation 1, 24, 48, and 72 hours after instillation, and then in weekly intervals up to day 28 post- instillation. The untreated left eye of each animal served as a control. The animals were 5 months old (3.61 -3.75 kg), and supplied by Centre Lago S.A. Vonnas, France.

Moderate conjunctival redness (grade 2), slight conjunctival chemosis (grade 1) and slight or moderate discharge (grade 1 or 2) were observed in all treated eyes 1 hour after application. Slight conjunctival redness (grade 1) was noted in a single animal at the 24-hours reading. In addition, injected scleral vessels in a circumscribed area were noted in all animals 1 hour after application. The ocular reactions were reversible in two animals within 24 to 48 hours after application. Mean scores calculated for each animal over 24, 48 and 72 hours were 0.0 for corneal opacity, iris lesions, and for chemosis; and 0.0, 0.3 and 0.0 for redness of the conjunctiva.

Using the individual scores presented in the Report, the mean irritation scores (MIS) and the maximum average score (MAS, mean of 24, 48, and 72 h scores) are as follows: MIS (maximum = 110) at 1, 24, 48, and 72 h were 8.7, 0.7, 0, and 0, respectively; MAS (maximum = 110) was 0.2.

In this study, the formulation was practically non-irritating. BAS 800 H is classified as EPA Toxicity Category IV for primary eye irritation.

This study is classified as acceptable. It does satisfy the guideline requirements for a primary eye irritation study (OPPTS 870.2400; OECD 405) in the rabbit.

COMPLIANCE: Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. **Test material:** BAS 800 H (N'-[2-chloro-4-fluoro-5-(3-methyl-2,6-dioxo-4-(trifluoromethyl)-3,6-dihydro-1(2H)-pyrimidinyl)benzoyl]-N-isopropyl-N-methylsulfamide)
   Description: Solid, light beige
   Lot/Batch #: COD-000515
   Purity: 93.8 % a.i.
   CAS #: 372137-35-4
   The homogeneity of BAS 800 H was confirmed by analysis. The stability under the storage conditions over the study period was guaranteed by the Certificate of Analysis.

2. **Vehicle and/or positive control:** No vehicle or positive control was used. The test substance was pulverized.

3. **Test animals:**

Species:	Rabbit (males)	
Strain:	New Zealand white A 1077 INRA (SPF)	
Age/weight at dosing:	Age: ~ 5 months; Weight: 3.61, 3.67, 3.75 kg	
Source:	Centre Lago S.A., 01540 Vonnas, France	
Housing:	Singly in stainless steel wire mesh cages with grating, floor area: 3000 cm^2	
Diet:	Kliba-Labordiat (Kaninchen & Meerschweinchenhaitung "GLP"), Provimi Kliba SA, Kaiseraugst, Basel Switzerland (about 130 g/animal per day)	
Water:	Tap water *ad libitum*	
Environmental conditions:	**Temperature:**	20 – 24°C
	Humidity:	30 -70%%
	Air changes:	10 air changes/h
	Photoperiod:	12 h dark/12 h light
Acclimation period:	At least 5 days before the beginning of the study.	

B. STUDY DESIGN and METHODS:

1. **In life dates** - Start: January 9, 2007 End: January 12, 2007

2. **Animal assignment and treatment** – An amount of 0.1 mL (~32 mg) of BAS 800 H was instilled into the conjunctival sac of the right eye of three male White New Zealand rabbits. About 24 hours after application, the eye was rinsed with tap water. The ocular reactions were assessed approximately 1, 24, 48, and 72 hours after application.

II. RESULTS AND DISCUSSION:

A. Irritation reaction: Moderate conjunctival redness (grade 2), slight conjunctival chemosis (grade 1) and slight or moderate discharge (grade 1 or 2) were observed in all treated eyes 1 hour after application. Slight conjunctival redness (grade 1) was noted in a single animal at the 24-hours reading. In addition, injected scleral vessels in a circumscribed area were noted in all animals 1 hour after application. The ocular reactions were reversible in two animals within 24 to 48 hours after application. Mean scores calculated for each animal over 24, 48 and 72 hours were 0.0 for corneal opacity, iris lesions, and for chemosis; and 0.0, 0.3 and 0.0 for redness of the conjunctiva.

Observations	Number "positive"/Number treated			
	1 hr	24 hrs	48 hrs	72 hrs
Corneal Opacity	0/3	0/3	0/3	0/3
Iritis	0/3	0/3	0/3	0/3
Conjunctivae				
Redness*	2/3	0/3	0/3	0/3
Chemosis*	0/3	0/3	0/3	0/3
Discharge	1/3	0/3	0/3	0/3
* Score of 2 or more required to be considered "positive"				

B. Authors' conclusions: *"Considering the described ocular reactions as well as the average score for irritation, BAS 800 H does not show an eye irritation potential under the test conditions chosen."*

C. Reviewer's comments: Using the individual scores presented in the Report, the mean irritation scores (MIS) and the maximum average score (MAS, mean of 24, 48, and 72 h scores) are as follows: MIS (maximum = 110) at 1, 24, 48, and 72 h were 8.7, 0.7, 0, and 0, respectively; MAS (maximum = 110) was 0.2.

D. Deficiencies: None.

Primary Reviewer: Steve Wong, Ph.D., PMRA **Date: March 10, 2008**
Secondary Reviewer: Rick Whiting, EPA
Risk Manager (EPA): 23

STUDY TYPE: Primary Dermal Irritation – Rabbit; OPPTS 870.2500; OECD 404

TEST MATERIAL: BAS 800 H; 93.9% a.i.; Batch No. COD-000298; light beige solid; stored at room temperature

CITATION: Remmele, M., Leibold, E.. (2005) BAS 800 H: Acute dermal irritation/ corrosion in rabbits. Study No. H0414/102293. Unpublished study by Experimental Toxicology and Ecology, BASF Aktiengesellschaft, Germany. May 9, 2005. MRID 47128106.

SPONSOR: BASF Corporation, Agricultural Products Division, RTP, NC 27709

EXECUTIVE SUMMARY: In a primary dermal irritation study (MRID 47128106), one male and two female New Zealand albino rabbits were dermally exposed for 4 hours to 0.5 g of BAS 800 H (93.9% a.i.; Batch No. COD-000298). The solid test substance was minimally moistened with doubly distilled water. Each dose was applied to the intact clipped skin using a test patch (2.5 cm x 2.5 cm) covered with semi-occlusive dressing. The test substance was removed with Lutrol® and Lutrol®/water after removal of the patch. Approximately 1, 24, 48, and 72 hours after removal of the patch, and then in weekly intervals maximally up to 14 days, the test sites of the skin were read using daylight tubes. The rabbits were between 7-8 months old and weighed between 3.79 and 4.02 kg. The animals were supplied by Centre Lago S.A. Vonnas, France.

Slight erythema was observed on all animals up to 1 hour after patch removal. The cutaneous reactions were reversible on all animals within 24 hours after removal of the patch. The average score (24 to 72 hours) for irritation was calculated to be 0.0 for erythema and edema.

In this study, the formulation was non-irritating. BAS 800 H is classified as EPA Toxicity Category IV for primary dermal irritation. Primary Irritation Index (PII) = 0.25.

This study is classified as acceptable. It does satisfy the guideline requirements for a primary dermal irritation study (OPPTS 870.2500; OECD 404) in the rabbit.

COMPLIANCE: Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. **Test material:** BAS 800 H (N'-[2-chloro-4-fluoro-5-(3-methyl-2,6-dioxo-4-(trifluoromethyl)-3,6-dihydro-1(2H)-pyrimidinyl)benzoyl]-N-isopropyl-N-methylsulfamide)

Description:	Solid, crystalline/light beige; stored at room temperature; pH (10% aqueous preparation) ≈ 4
Lot/Batch #:	COD-000298
Purity:	93.9% a.i.
CAS #:	372137-35-4
	The homogeneity of BAS 800 H was confirmed by analysis. The stability under the storage conditions over the study period was guaranteed by the Certificate of Analysis.

2. Vehicle and/or positive control: No vehicle or positive control was used. Immediately before test-substance application, the solid test substance was minimally moistened with a suitable amount of doubly distilled water to guarantee skin contact.

3. **Test animals:**

Species:	Rabbit (one male and two females)	
Strain:	New Zealand white A 1077 INRA (SPF)	
Age/weight at treatment:	Age: 7-8 months; Weight: ♂ = 3.79; ♀ = 3.85 and 4.02 kg	
Source:	Centre Lago S.A., 01540 Vonnas, France	
Housing:	Singly in stainless steel wire mesh cages with grating, floor area: 3000 cm^2	
Diet:	Kliba-Labordiat (Kaninchen & Meerschweinchenhaitung "GLP"), Provimi Kliba SA, Kaiseraugst, Basel Switzerland (~130 g/rabbit/d)	
Water:	Tap water *ad libitum*	
Environmental conditions:	**Temperature:**	20 – 24°C
	Humidity:	30 - 70%
	Air changes:	10 air changes/h
	Photoperiod:	12 h dark/12 h light
Acclimation period:	At least 5 days before the beginning of the study.	

B. STUDY DESIGN and METHODS:

1. In life dates - Start: November 9, 2004 End: November 12, 2004

2. Animal assignment and treatment – At least 24 hours before the beginning of the study, the dorso-lateral part of the trunk of the animals (two females and one male) was clipped. Immediately before test substance application, the solid test substance, BAS 800 H, was minimally moistened with a suitable amount of doubly-distilled water to guarantee skin contact. The test substance was applied for four hours as a single dose to the intact untreated skin of the flank of the rabbits. The test patch was secured in position with a semi-occlusive dressing. The test patch (2.5 x 2.5 cm^2) was covered with an amount of minimally moistened solid preparation, corresponding to a dose of 0.5 g of unchanged test substance. The rabbits were weighed just before application of the test substance and after the last reading. They were checked for mortality or moribundity twice each workday (beginning and end) and once on weekends and on holidays. After exposure, the test patch was removed and the test skin area was cleaned with Lutrol® (polyethylenglycol) and Lutrol®/water (1:1).

II. RESULTS AND DISCUSSION:

A. Skin reaction: Slight erythema (grade 1) was observed in all rabbits up to 1 hour after removal of the patch. The skin reactions were reversible in all animals within 24 hours. Mean scores over 24, 48, and 72 hours for each animal were 0 for erythema and for edema.

INDIVIDUAL SKIN IRRITATION SCORES

ERYTHEMA/EDEMA

Animal Number	Sex	Time observed				
		0 to 1 hr	24 hrs	48 hrs	72 hrs	Day 7
01	F	1/0	0/0	0/0	0/0	0/0
02	M	1/0	0/0	0/0	0/0	0/0
03	F	1/0	0/0	0/0	0/0	0/0
Severity of Irritation – Mean Score		0.3/0	0/0	0/0	0/0	0/0

B. Authors' conclusions: *"Considering the described cutaneous reactions as well as the average score for irritation, BAS 800 H does not show a skin irritation potential under the test conditions chosen."*

C. Deficiencies: None.

Primary Reviewer: Steve Wong, Ph.D., PMRA **Date: March 12, 2008**
Secondary Reviewer: Rick Whiting, EPA
Risk Manager (EPA): 23

STUDY TYPE: Dermal Sensitization – Guinea Pig; OPPTS 870.2600; OECD 406

TEST MATERIAL: BAS 800 H; 93.8% a.i.; Batch No. COD-000515; light beige solid

CITATION: Gamer, A.O., Leibold, E. (2005) BAS 800 H: Maximization test in guinea pigs. Study No. 30H0414/012302. Unpublished study by Experimental Toxicology and Ecology, BASF Aktiengesellschaft, Germany. August 8, 2005. MRID 47128107.

SPONSOR: BASF Corporation, Agricultural Products Division, RTP, NC 27709

EXECUTIVE SUMMARY: In a dermal sensitization study (MRID 47128107) with BAS 800 H (93.8% a.i.; Batch No. COD-000515), 15 female HsdPoc: DH guinea pigs were tested using the maximization test. The test substance was applied as a suspension for intradermal application and on a dry paste for the epicutaneous induction and challenge application. The intradermal induction was performed with a 5% test substance preparation in 1% CMC-solution in doubly distilled water or 5% test substance preparation in Freund's complete adjuvant (FCA) / 0.9% aqueous NaCl-solution (1:1). One week following the intradermal induction, the epicutaneous induction with a 50% test substance preparation in 1% CMC-solution in doubly distilled water was carried out. Gauze patches (2 cm x 4 cm) containing 50% of test substance prepared in 1% CMC-solution in double distilled water was applied to the clipped skin of the neck region under an occlusive dressing consisting of rubberized linen patches and Fixomull stretch adhesive fleece. The patch remained on the skin for 48 hours and the skin was evaluated immediately after patch removal. For the challenge, a 25% test substance preparation in 1% CMC-solution in doubly distilled water was applied to the test site (right flank) 14 days after the epicutaneous induction. Reactions were scored 24 and 48 hours after test material applications. The neck and flank regions were clipped at least 2 hours before each test substance application and if necessary, at least 2 hours before skin evaluation. The test substance was removed with water. The guinea pigs were between 7-8 weeks old and weighed between 438 and 514 g at the start of the study. The animals were supplied by Harlan Winkelmann, Germany.

The intradermal induction caused moderate and confluent to intense erythema and edema at the injection sites of the test substance in all treated animals. After the epicutaneous induction, partially open incrustation was observed in addition to moderate and confluent erythema and swelling in all treated animals. No skin findings after challenge were observed on the treated animals.

Based on the results of this study, BAS 800 H was *not* a dermal sensitizer.

This study is classified as acceptable. It does satisfy the guideline requirements for a dermal sensitization study (OPPTS 870.2600; OECD 406) in the guinea pigs.

COMPLIANCE: Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1.	**Test material:**	BAS 800 H (N'-[2-chloro-4-fluoro-5-(3-methyl-2,6-dioxo-4-(trifluoromethyl)-3,6-dihydro-1(2H)-pyrimidinyl)benzoyl]-N-isopropyl-N-methylsulfamide)
	Description:	Solid, light beige (information from other study reports)
	Lot/Batch #:	COD-000515
	Purity:	93.8% a.i.
	CAS #:	372137-35-4
		The homogeneity of the test material was confirmed by analysis. The stability under the storage conditions over the study period was guaranteed by the Certificate of Analysis.

2. Vehicle and/or positive control: sodium carboxymethylcellulose (1% CMC) in doubly distilled water.

3.	**Test animals:**	Guinea pig (females)	
	Strain:	HsdPoc:DH For the intradermal pretest animals of the strain/quality "Dunkin Hartley, Crl:HA" of the supplier, Charles river Deutschland GmbH, Stolzenseeweg 32 – 36, 888353 Kisslegg were used.	
	Age/weight at start:	Age: 7 – 8 weeks; Weight: 438 – 514 g	
	Source:	Harlan Winkelmann, gartenstr 27, 33178 Borchen, Germany	
	Housing:	5 per cage; stainless steel wire mesh cages with plastic-coated grating, minimum floor area: 2,000 cm^2	
	Diet:	Kliba Labordiät (Kaninchen/Meerschweinchen-Haltungsdiät) Provimi Kliba SA, Kaiseraugst, Switzerland *ad libitum*	
	Water:	Tap water *ad libitum*	
	Environmental conditions:	**Temperature:**	20 – 24°C
		Humidity:	30 -70 %
		Air changes:	10 air changes/h
		Photoperiod:	12 h dark/12 h light
	Acclimation period:	14 days before the first test substance application	

B. STUDY DESIGN and METHODS:

1. In life dates - Start: March 11, 2005 End: April 8, 2005

2. Animal assignment and treatment – The study consisted of pretests and a main test. The concentrations for BAS 800 H used in the main test were determined in the pretests. The animals were distributed to the individual groups according to the randomization instructions of "Nijenhuis, A. and Wilf, H.S. (1978): Combinatorial Algorithms, Academic Press, New York, San Francisco, London. At least 2 hours before each test substance application, the fur at the application sites was clipped. If necessary, the test skin sites were clipped free of hair before evaluation of skin reaction. All animals were checked for clinical signs and mortality twice daily on weekdays and once on weekends and holidays.

Animal assignment is given in the following table.

	Pre-test		Main study	
	Intradermal	Percutaneous	Control group	Test group
Number of animals used, N	2	3	5	10
Intradermal induction injection				
Intra: 0.1 mL FCA : saline (1:1)	√	√	√	√
Intra: 0.1 mL BAS 800H in 1% CMC	√		√	√
Intra: 0.1 mL BAS 800H in FCA (1 :1) : saline (1:1)	√			√
Intra: 0.1 mL of 1% CMC			√	
Per : 0.5 mL of 50 and 25% in 1% CMC		√ Per treatment 3 weeks after Intra treatment	Per induction 1 week after Intra induction	
Percutaneous induction application				
Per : 1 mL (~1 g) in 1% CMC			√	√
			Per challenge 2 weeks after Per induction	
Percutaneous challenge application				
Per challenge : 0.5 mL of 25% BAS 800H in 1% CMC			√	√
Assessment of skin reaction, h after treatment	24	1, 24, 48	24 after Intra induction 48 after Per induction 24 & 48 after Per challenge	
Intra = intradermal injection; Per = percutaneous; FCA = Freund's complete adjuvant				

Test substance preparation: Prior to its use, BAS 800H was ground with pestle and mortar. Cleaned 1% CMC in doubly distilled water was used as vehicle because good homogeneity of the preparation was achieved. The BAS 800 H preparations were produced on a weight by weight (w/w) basis shortly before the application by stirring with a high speed homogenizer and a magnetic stirrer. BAS 800H was applied as a suspension for intradermal application and for percutaneous challenge application and as a dry paste for the percutaneous induction application.

Intradermal pretest: A concentration of BAS 800H that was well-tolerated locally and systemically was chosen for the intradermal induction treatment in the main test. Three pairs of intradermal injections were applied to the neck region of each animal (2 animals per test substance concentration):

A) front row: 2 injections each of 0.1 mL Freund's complete adjuvant (FCA) without test emulsified with 0.9% aqueous NaCl-solution in a ratio of 1:1.
B) middle row: 2 injections each of 0.1 mL of a test substance formulation in an appropriate vehicle at the selected concentration.
C) back row: 2 injections each of 0.1 mL FCA/0.9% aqueous NaCl-solution (1:1) with test substance at the selected concentration.

Skin reaction was assessed 24 h after the beginning of application.

Percutaneous pretest: For the dermal induction, the highest concentration of BAS 800H that caused slight to moderate irritation and for the challenge, the maximum non-irritant concentration was determined with the pretest. For detecting a possible influence on irritating effects of previous intradermal treatment with FCA, animals were pretreated with FCA/0.9% aqueous NaCl-solution (1:1) each, in the front row (A) and back row (C) without test substance about 3 weeks prior to the application of the test substance, were used. Gauze patches (2x2 cm; 6 layers surgical gauze) containing 0.5 mL or 0.5 g of BAS 800 H preparation were applied to the skin of the flanks under an occlusive dressing. The dressing consisted of rubberized linen patches (4 x 4 cm), patches of Indealbinde™ (5 x 5 cm), and adhesive fleece. Three animals were used for each BAS 800 H concentration; exposure was for 24 h; skin reactions were assessed at 1, 24, and 48 h after removal of the patches.

Main Test: Five animals in control and 10 animals in test group.

A. Induction

Intradermal inductions: Three pairs of intradermal induction per animal were given to the neck region. Reactions were assessed 24 h after the beginning of application.

Injections for the control group are as follows:
A) front row: 2 injections each of 0.1 mL FCA without test emulsified with 0.9% aqueous NaCl-solution in a ratio of 1:1.
B) middle row: 2 injections each of 0.1 mL of the undiluted vehicle.
C) back row: 2 injections each of 0.1 mL of a 50% formulation of the vehicle without test substance emulsified with FCA/0.9% aqueous NaCl-solution (1:1).

Injections for the test group are as follows:
A) front row: 2 injections each of 0.1 mL FCA without test emulsified with 0.9% aqueous NaCl-solution in a ratio of 1:1.
B) middle row: 2 injections each of 0.1 mL of a test substance formulation in an appropriate vehicle at the selected concentration.
C) back row: 2 injections each of 0.1 mL FCA/0.9% aqueous NaCl-solution (1:1) with test substance at the selected concentration.

Percutaneous induction: Percutaneous induction was conducted one week after intradermal induction. Gauze patches (2x4 cm; 6 layers surgical gauze) containing the 50% BAS 800H preparation in CMC were applied to the skin of the neck region under an occlusive dressing. The dressing consisted of rubberized linen patches (4 x 6 cm) and an adhesive fleece. Exposure was for 48 h and skin reactions were assessed immediately after removal of the patch.

B. Challenge – The percutaneous challenge was performed 14 days after the percutaneous induction. Gauzes (6 layers surgical gauze, 2x2 cm^2) containing the 25% BAS 800H preparation in CMC were applied to the intact skin of the flank under an occlusive dressing. The dressing consisted of rubberized linen patches (4 x 4 cm), patches of Idealbinde™ (5 x 5 cm), and an adhesive fleece. An amount of 0.5 mL of the BAS 800H preparation was applied to each animal in both the test and control groups. Exposure was for 24 h and skin reactions were assessed at 24 and 48 h after the removal of the patch.

Positive control: A positive control (reliability check) with a known sensitizer was not included in this study. However, separate positive control studies were performed twice a year in the laboratory. The positive controls with α-hexylcinnamaldehyde (85%) showed that the test system was able to detect sensitizing compounds under the laboratory conditions chosen. The results of the most recent positive control studies were included in the Report.

II. RESULTS AND DISCUSSION:

A. Pre-tests:

Intradermal – Injections with FCA/saline and injections with 5% BAS 800 H preparation in FCA/0.9% resulted in grade 3 reactions (intense erythema and swelling). Injection of the 5% BAS 800 H preparation in CMC resulted in grade 2 reaction (moderate and confluent erythema) with swelling.

Percutaneous – Percutaneous application of a 50% BAS 800 H preparation in CMC resulted in grade 2 reaction (moderate and confluent erythema) at 1 h and a grade 1 reaction (discrete or patchy erythema) at 24 h. A 25% preparation of BAS 800 H caused grade 1-2 reaction at 1 h only. No skin reactions were evident at 24 h with the 25% BAS 800 H preparation or at 48 h with the 50% preparation.

B. Main study:

Intradermal induction - After the intradermal induction, intense erythema and swelling were observed at the injection sites of all control and test animals at which only FCA/0.9% aqueous NaCl-solution (1:1) was applied. At the injection sites of a 5% BAS 800 H preparation in FCA/0.9% aqueous NaCl-solution (1:1) intense erythema and swelling were seen in all test animals. Injections of a 5% BAS 800 H preparation in 1% CMC-solution in doubly distilled water caused moderate and confluent erythema and swelling in all test animals. The control animals, injected with 1% CMC-solution in doubly distilled water showed no skin reactions. A 50% formulation of 1% CMC-solution in doubly distilled water with FCA/0.9% aqueous NaCl-solution (1:1) caused intense erythema and swelling in all control animals.

Control group - Skin reactions 24 h after the beginning of application

Animal	Application Site	Intradermal injection (in neck region) of		
		A) FCA/0.9% aqueous NaCl solution (1:1)	B) 1% CMC solutions	C) 50% formulation of 1% CMC solution with FCA/0.9% aqueous NaCl solution (1:1)
All animals	right	3	0	3
	left	3	0	3

3 = intense erythema and swelling

Test group - Skin reactions 24 h after the beginning of application

Animal	Application Site	Intradermal injection (in neck region) of		
		A) FCA/0.9% aqueous NaCl solution (1:1)	B) 1% CMC solutions	C) 50% formulation of 1% CMC-solution with FCA/0.9% aqueous NaCl solution (1:1)
All animals (N = 10)	right	3	2E	3
	left	3	2E	3

2 = moderate and confluent erythema; 3 = intense erythema and swelling; E = swelling

Percutaneous inductions -
The percutaneous induction with a 50% BAS 800 H preparation in CMC, led to incrustation, partially open (caused by the intradermal induction) and moderate and confluent erythema and swelling in all test group animals.

Test group - Skin reactions directly after removal of the patch

Animal	Percutaneous application (in neck region) of 50% BAS 800 H in 1% CMC
All animals (N = 10)	2 E K (moderate and confluent erythema; swelling; incrustation, partially open

Challenge application – The challenge with a 25% BAS 800H preparation in CMC did not cause any skin reactions in any control or test animals 24 and 48 h after removal of the patches. Since no borderline results were observed, a 2nd challenge was not performed.

Control group - Skin reactions 24 and 48 h after removal of the patch

	Percutaneous application (in middle right flank region) of 25% BAS 800 H in CMC	
Animal	24 h	48 h
All animals (N= 5)	0	0

Test group - Skin reactions 24 and 48 h after removal of the patch

	Percutaneous application (in middle right flank region) of 25% BAS 800 H in CMC	
Animal	24 h	48 h
All animals (N = 10)	0	0

Test substance was removed with water.

C. Positive control – A positive control with a known sensitizer was not included in this study. However, a separate study was performed twice a year in the laboratory. The positive controls with α-hexylcinnam-aldehyde (technical, 85%) showed that the test system was able to detect sensitizing compounds under the laboratory conditions chosen. The number of animals with skin findings after the challenge is summarized in the following two tables.

Maximization Test (October 1, 2004 – January 6, 2005)

	Challenge					
	α-hexylcinnamaldehyde 5% In Lutrol® E 400			Vehicle control In Lutrol® E 400		
	24 h	48 h	Total	24 h	48 h	Total
Control Group	0/5	0/5	0/5	0/5	0/5	0/5
Test Group	10/10	9/10	10/10	0/10	0/10	0/10

x/y: number of positive reactions/number of animals tested (reading at 24 hours and 48 hours after the removal of the patch)

Modified Buehler Test (January 7, 2005 – February 22, 2005)

	Challenge					
	α-hexylcinnamaldehyde 15% In Lutrol® E 400			Vehicle control In Lutrol® E 400		
	24 h	48 h	Total	24 h	48 h	Total
Control Group	0/10	0/10	0/10	0/10	0/10	0/10
Test Group	19/20	16/20	19/20	0/20	0/20	0/20

x/y: number of positive reactions/number of animals tested (reading at 24 hours and 48 hours after the removal of the patch)

D. Authors' conclusions: *"Based on the evaluation criteria cited ..., the results of this study show that BAS 800 H does not have a sensitizing effect on the skin of the guinea pig in the Maximization Test under the test conditions chosen."*

E. Deficiencies: None.

ACUTE TOX ONE-LINERS

1. **DP BARCODE:** D349940
2. **PC CODE:** 118203
3. **CURRENT DATE:** 21/JUL/2009
4. **TEST MATERIAL:** BAS 800 H; 93.8% a.i.; Batch No. COD-000515; light beige solid; expiry date: February 1, 2006

Study/Species/Lab Study # /Date	MRID	Results	Tox. Cat.	Core Grade
Acute oral toxicity / rat Experimental Toxicology & Ecology 10A0414/011124 August 8, 2005	47128101	LD_{50} > 2000 mg/kg (females)	III	A
Acute dermal toxicity / rat Experimental Toxicology & Ecology 11A0414/011125 / August 8, 2005	47128102	LD_{50} > 2000 mg/kg (males and females)	III	A
Acute inhalation toxicity / rat Experimental Toxicology & Ecology 13I0414/017021 / August 20, 2005	47128103	LC_{50} > 5.3 mg/L (males and females)	IV	A
Primary eye irritation / rabbit Experimental Toxicology & Ecology 11H0414/102297 / May 9, 2005	47128104	Practically non- irritating	IV	A
Primary eye irritation / rabbit Experimental Toxicology & Ecology 11H0414/012309 / May 3, 2005	47128105	Practically non- irritating	IV	A
Primary dermal irritation / rabbit Experimental Toxicology & Ecology 18H0414/102293 / May 9, 2005	47128106	Non- irritating	IV	A
Dermal sensitization / guinea pig Experimental Toxicology & Ecology 30H0414/012302 / August 8, 2005	47128107	Negative	---	A

Core Grade Key: A =Acceptable, S = Supplementary, U = Unacceptable, W = Waived